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Lornoxicam

Expert Statement

Expert Meeting on 3rd April 2003

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Foreword

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For half a century now, NSAID have been an indivisible part of medicinal treatment for diseases of the musculoskeletal system. However, effective medications possess different side effects profiles. NSAID are frequently administered as long-term therapy. Therefore, the risk of side effects must be included in the therapeutic concept. For several decades, pharmacological research has been making efforts to develop substances that can be tolerated better while providing analgesic, anti-phlogistic and anti-pyretic effects. Lornoxicam is a product developed by Professor Dieter Binder in Austria that fulfils these requirements.

Based on the available data and clinical experience concerning lornoxicam, an interdisciplinary committee produced the following expert statement. The statement is a consensus of experts concerning the profile of action and clinical application of lornoxicam.
As Professor Dieter Binder who was involved in this project expired suddenly while it was in progress, the present expert statement is dedicated to him.

With best wishes,

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Prim. Univ.-Prof. Dr. Wilfried Ilias

Mag. Andrea Budin, Medizin Akademie

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In memory of Univ.-Prof. Dr. Dieter Binder

Dieter Binder, a retired university professor of organic chemistry, was certainly the most successful pharmaceutical researcher in Austria during the last few decades. He introduced three products in the market; one of these was lornoxicam. Late in his life Professor Binder became a student of Otto Hromatka.
Together with Hromatka, Binder shifted his focus of work to pharmaceutical research late in life and was very successful in this endeavour. He was recognized internationally for his work. Brotizolame, a benzodiazepine with a large market share particularly in Japan, was developed by Binder and now achieves a turnover of about one billion dollars per year. Binder acquired great merit for himself and his institute especially in the field of research on the thiophene ring and its possibilities of substitution, which allow a very accurate tuning of its pharmacological effects. Lornoxicam is one of the several outcomes of this research. Binder's philosophy was to conduct targeted research based on intelligent, well reasoned concepts. This approach was probably one of the many reasons why he was successful.
Until his sudden demise on 17th February 2003 Binder was fully committed to, and actively working on a number of innovative projects.
Dieter Binder was also involved in formulating the concept of this expert statement. Therefore, all persons involved in this project would like to dedicate this expert statement to him. We pay homage to Dieter Binder, one of the most original researchers in Austria. He will always be remembered as a unique individual and an outstanding Austrian researcher.

O. Univ.-Prof. Dr. Christian Roland Noe

Lornoxicam

1. Introduction

The spectrum of action of so-called non-steroidal inflammatory drugs (NSAID) includes analgesic, anti-phlogistic and anti-pyretic effects; all of these are still very important in medicine. Research concerning the complex effects of NSAID is by no means complete, as clearly revealed by the ongoing discussion about the role of isoenzymes of cyclooxygenase (COX), the most important point of action for NSAID.

Representatives of this drug group are the most frequently prescribed analgesics. It is the combination of the above mentioned properties of action that makes this drug group so important. Several types of pain are associated with an inflammatory process and it is very appropriate to use these substances for such conditions. However, as the rate of side effects is rather high particularly for this drug category, the medications should be used with great caution.

The necessity to switch to a different NSAID of this group if a patient does not tolerate one product justifies the continued effort to develop new substances of this group.

Lornoxicam inhibits the COX-1/COX-2 system, the production of interleukin-6, and the inducible NO synthase [1]. It may be applied by the intramuscular or intravenous route; its bioavailability after oral application is approximately 90%. Although its elimination half-life is only about four hours [2], the duration of effect is approximately eight hours, analogous to other acidic anti-pyretic analgesics. The analgesic potency of lornoxicam is remarkable. In doses of 16mg (i.m.) its analgesic effect is comparable with that of 20mg morphine (i.m.) or 50mg tramadol (i.v) [3,4].

The principal clinical indications for lornoxicam are rheumatic diseases and perioperative pain management.

2. Non-steroidal anti-inflammatory drugs

2.1. Effects of NSAID

NSAID have analgesic, anti-pyretic and anti-phlogistic effects. The most important mechanism responsible for all three effects is the inhibition of cyclooxygenase and, subsequently, the reduced production of prostaglandins. Prostaglandins (primarily prostaglandin E2) sensitise the nocireceptors in the damaged tissue without triggering pain themselves. The blockade of prostaglandin synthesis leads to a peripheral as well as central inhibition of pain. The principal effect in the inflamed tissue is that the sensitisation of pain receptors is inhibited while the main effect in the central nervous system is the inhibition of synaptic transmission.

2.2. Isoenzymes of cyclooxygenase

Isoenzymes of cyclooxygenase (COX) were discovered at the beginning of the 1990s. COX-1 is constitutively expressed in nearly all cell types, including those in the kidney, stomach, thrombocytes and vascular endothelium. It is a so-called house-keeping enzyme that regulates physiological adaptations. COX-2 is induced during tissue damage and inflammations by cytokines such as tumor necrosis factor α, interleukin 1, mitogens and growth factors. The induction of COX-2 has been observed in macrophages, endothelial cells, thrombocytes and osteoblasts. Elevated levels of COX-2 have also been registered in the synovial tissue of patients with rheumatoid arthritis and osteoarthritis [5]. Glucocorticoids can inhibit the induction of COX-2 synthesis; anti-inflammatory cytokines such as IL-4, IL-10 and IL-13 also inhibit the production of COX-2. These findings led to the hypothesis that selective inhibition of COX-2 for the treatment of inflammation and pain would have less effects on the gastrointestinal tract, the kidney, and blood coagulation. Contrary to the original thesis, it was found that COX-2 also plays a significant role in gastric mucosal protection. Thus, it may be concluded that in the presence of ulcers, even if the patient is being treated with pure COX-2 inhibitors, a proton pump inhibitor is indicated. With regard to the kidney it was found that COX-2 is constitutively present here as well. As platelet aggregation is exclusively activated through COX-1, the ability of NSAID to inhibit COX-1 under specific circumstances is also rated very positively.

Furthermore, COX-2 is constitutively expressed in nerve cells of all layers of the spinal cord. In patients with a peripheral inflammation, e.g. in a joint, COX-2 is upregulated bilaterally in the spinal cord even in the presence of unilateral inflammation. In peripheral nerve injuries COX-2 is expressed in neuronal as well as non-neuronal cells of the spinal cord. The enhanced expression of COX-2 in the spinal cord increases the basic, as well as inflammatory release of prostaglandins. Based on these conclusions, the spinal cord is an important point of action for the effect of NSAID. The release of prostaglandins secondary to in-

flammatory processes leads to hyperalgesia through the spinal cord; NSAID inhibit the release of PGE2 and reduce hyperalgesia [6].
The discovery of a variant of COX-1, named COX-3 by the authors, is inhibited by paracetamol, phenacetine and metamizole. This variant also gives rise to speculations about the mechanism of action of these substances, whose effects have not been clearly explained to the present day [7].

2.3 Side effects

The majority of the side effects of NSAID also can be explained by the inhibition of prostaglandin synthesis [8]. Therefore, the indication for long-term NSAID treatment should be established with caution. The side effects mainly concern the gastrointestinal tract. The symptoms may be harmless, such as nausea, stomach pain or acute haemorrhage in the gastric mucosa, or even dangerous such as ulcerations with perforation and life-threatening gastrointestinal haemorrhage.
Therefore, patients at risk (Table 1) should be given appropriate gastric protection (Table 2) [9]. Further side effects of NSAID are disturbances of renal function, inhibition of platelet aggregation, skin reactions and pseudo-allergic reactions with bronchospasm (aspirin-induced asthma).
In respect of interactions with other drugs, especially those with oral anticoagulants and anti-diabetic drugs should be kept in mind.
Their plasma protein binding is suppressed by NSAID, resulting in a higher risk of haemorrhage and/or hypoglycaemia. Furthermore, NSAID may interact with anti-hypertensive drugs such as ACE inhibitors, whose anti-hypertensive effect may be weakened [10]. NSAID are contraindicated in patients with gastrointestinal ulcers, women in the third trimester of pregnancy, and during lactation. In addition to peripheral side effects NSAID may have central side effects such as fatigue.

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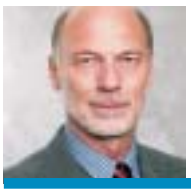

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2.4. The value of NSAID in rheumatology

NSAID are first-choice drugs in rheumatology. In the USA alone, about 30 million individuals use one or more NSAID.
In Austria, between July 2000 and June 2001 about 2.9 million prescriptions for NSAID were issued. Thus, NSAID obviously constitute a significant cost factor in medicine.

Of the wide range of effects of NSAID – anti-inflammatory, analgesic and anti-pyretic – the anti-inflammatory and analgesic effects are of importance in clinical rheumatology. It should be noted that the efficacy of individual substances may differ from patient to patient.

In principle, when treatment with NSAID is indicated in rheumatology, monotherapy should be given preference. The selected drug may well be used in the highest approved dose.

NSAID reduce signs (such as swelling and reddening) and symptoms (such as pain) of joint inflammation. However, they are unable to eliminate the cause of the inflammation. In patients with inflammatory rheumatic diseases they do not intervene in the disease process; hence they do not belong to the category of disease-modifying drugs.
The efficacy of NSAID in different rheumatic diseases has been proved according to the criteria of evidence-based medicine. In cases of osteoarthritis the patient should first be given paracetamol; only if this is ineffective a NSAID should be prescribed [11].

The efficacy of NSAID in rheumatology has been conclusively proven for rheumatoid arthritis, spondylarthropathy, sero-negative spondylarthritis, gout, osteoarthritis and collagen disease (lupus erythematosus/LE).
Furthermore, NSAID have been successfully used in patients with psoriatic arthritis or reactive arthritis. The

Table 1:
Risk factors for patients under NSAID therapy [9]

- Age above 65 years
- History of ulcers
- Simultaneous long-term therapy with corticosteroids
- Simultaneous administration of acetylsalicylic acid
- Simultaneous therapy with anticoagulants

Table 2:
Primary prophylaxis for NSAID-induced gastropathy

The following procedure is recommended for patients with risk factors for NSAID-induced gastropathy
Gastric protection with
1. PPI (e.g. pantoprazole or omeprazole 20mg/die)
2. Misoprostol 4x200mcg/die
3. Farnotidine 2x40mg/die

Figure 1:
Approximately isopotent inhibition of COX-1 and COX-2 by lornoxicam (in vitro) [1]

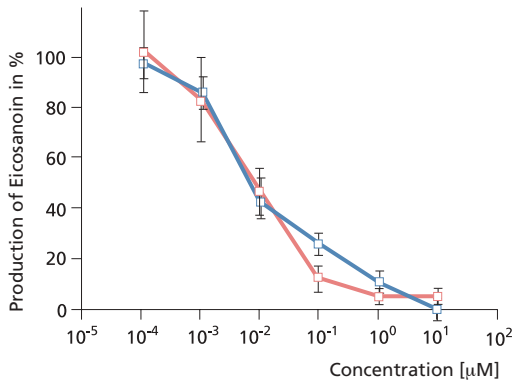
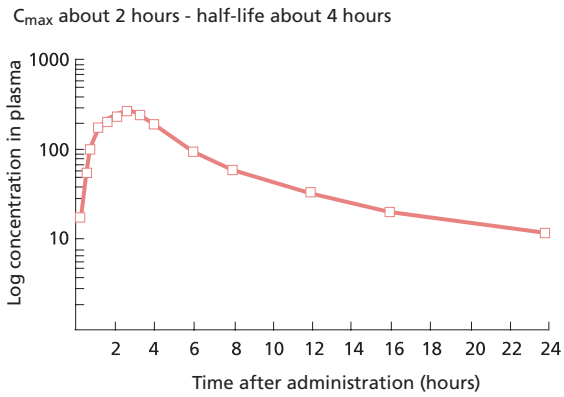


Figure 3:
Pharmacokinetics of lornoxicam in healthy persons [2, 14]



analgesic effect may be monitored with the aid of visual analogue scales, which allow an objective assessment of pain relief. Quite often pain is relieved even with doses of NSAID that are insufficient to achieve an anti-inflammatory effect.

3. Lornoxicam

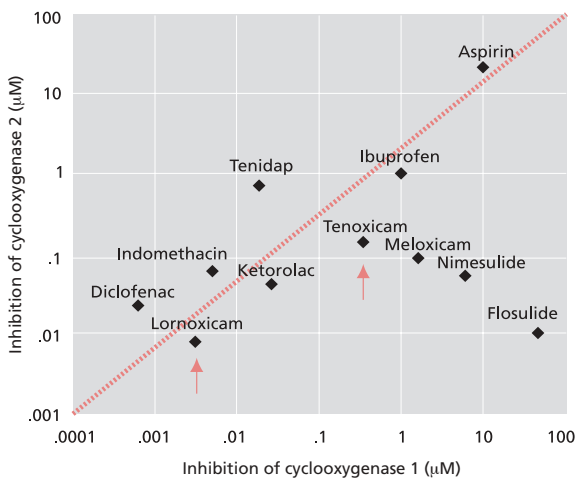
3.1 Pharmacology of Lornoxicam

3.1.1 Pharmacodynamics

Lornoxicam is an active substance from the group of acidic anti-pyretic analgesics. The accumulation of acidic analgesics in the inflamed tissue is considered to be a significant aspect of their anti-inflammatory effect. In cases of painful inflammatory reactions, the capillaries in the inflamed tissue are damaged and plasma proteins along with bound pharmaceutical substances are discharged into the extravascular space.

On account of the reduced pH value in inflamed tissue, analgesic acids are able to move from the extracellular space and enter the cells more easily. This also explains why the duration of action of acidic substances is generally longer than one would expect in consideration of their plasma half-life.
The inflamed tissue probably behaves like a deep compartment whose filling and depletion adjust to the plasma concentrations with substantial delay [12].

Figure 2:
Potent inhibition of both COX isoenzymes by lornoxicam [13]



Like all other NSAID lornoxicam's mechanism of action is based on the inhibition of cyclooxygenase (COX); an almost equivalent inhibition of COX-1 and COX-2 is achieved (see Figure 1).

Lornoxicam's potency of effect on the two COX isoenzymes in vitro is similar to that of diclofenac and about two powers of ten stronger than that of tenoxicam (see Figure 2).

3.1.2. Pharmacokinetics

The bioavailability of lornoxicam after oral application is more than 90%. Maximum plasma concentrations are achieved after about two hours. Given normal liver and kidney function, the plasma half-life is about four hours (see Figure 3). In elderly patients the clearance of lornoxicam is reduced by about 30% to 40%; thus the half-life is somewhat longer. Even in the presence of impaired kidney and liver function, no major differences in pharmacokinetics have been observed.
On account of its short half-life, no accumulation is likely to occur even in cases of repeated administration – in contrast to NSAID with a longer half-life. Like other oxicams and diclofenac, lornoxicam is metabolised via cytochrome P450 (CYP-2C9). Due to a genetic polymorphism some individuals may metabolise slowly and therefore have elevated levels of lornoxicam.

3.1.3 Interactions

Plasma concentrations of lornoxicam and many other NSAID are increased by cimetidine but not by ranitidine. Lornoxicam reduces the renal clearance of digoxin. Lornoxicam may also increase serum concentrations of methotrexate

and cyclosporine. Interactions with CYP-2C9 inducers (e.g., rifampicin) may also occur.

3.1.4 Tolerability

In large studies 16% of patients experienced gastrointestinal intolerance [15]. Thus, lornoxicam is well within the range of many non-selective NSAID. The other side effects of lornoxicam are mild. In general lornoxicam is a NSAID with a typical side effect profile. With regard to disturbances of renal and hepatic function, lornoxicam compares well with other NSAID (see Figures 4 and 5). No major increases in kidney or liver data have been observed with lornoxicam. Nevertheless, caution should be exercised when using NSAID and also lornoxicam to treat patients with impaired liver or kidney function. The short half-life of lornoxicam is an advantage in patients with impaired renal function because it offers recovery phases for the kidney between the individual doses. In clinical practice the increase in the volume of extracellular fluid secondary to NSAID is significant because it may lead to cardiac problems in predisposed patients.

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3.1.5 Control of renal function

When lornoxicam is administered, renal function should be controlled in specific situations (see Table 3); this applies to many other NSAID as well.
It should be noted that only creatinine clearance allows a truly adequate assessment of renal function. The simultaneous administration of NSAID and heparin during spinal or epidural anaesthesia increases the risk of spinal/epidural haematoma.

3.2 Clinical indications

The efficacy of lornoxicam has been proven in patients with rheumatoid arthritis, in those with ankylosing spondylitis, osteoarthritis, chronic back pain, disk prolapse, or other orthopaedic problems, as well as in general and perioperative pain management.

3.2.1 Rheumatoid arthritis

In a randomised double-blind trial [17], lornoxicam administered at a dose of 3x4mg was compared with diclofenac 3x50mg for three weeks in 316 patients with rheumatoid arthritis. The mean age of the subjects was 55 years and the duration of the disease, six to seven years. Both substances were equally effective with regard to various functional parameters such as the Ritchie index, the visual analogue scale (VAS), morning stiffness (MSK) and fist closure (FSK) (see Figure 6).

In clinical practice it was found that, based on its quantity in milligrams, lornoxicam is a lesser load for the organism than the majority of NSAID, while it possesses the same efficacy profile with regard to its action on cyclooxygenases (also see Figures 4 and 5).
Lornoxicam concentrations in the synovial fluid of patients with rheumatoid arthritis or gonarthrosis are approximately 50% of its concentration in plasma, which is a well acceptable ratio for the management of arthritis.
Lornoxicam concentrations in the synovia are reduced parallel to plasma concentrations and drop to the non-therapeutic range after about eight hours.

3.2.2 Arthrosis (osteoarthritis)

Both Austrian and international guidelines [18] recommend the use of NSAID in osteoarthritis from the stage of painful osteoarthritis onward. Lornoxicam is effective in doses of 12mg and 16mg per day in patients with osteoarthritis of the hip and the knee; the safety and tolerability profiles of lornoxicam are comparable to those of diclofenac.

Figure 4:
Changes in kidney parameters under various NSAID [16]

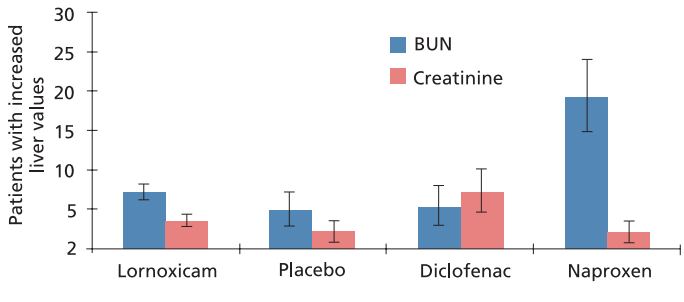
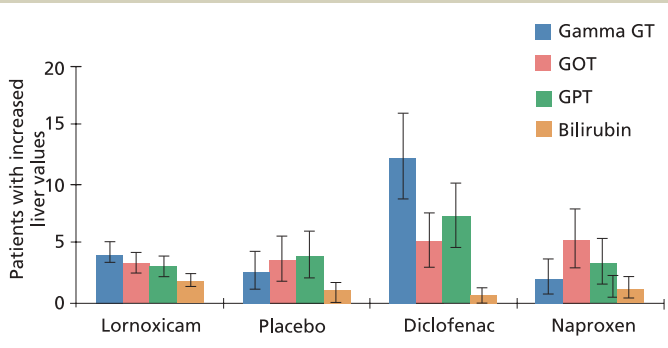


Figure 5:
Changes in liver parameters under various NSAID [16]



Two studies are significant with regard to the use of lornoxicam for this indication. In one double-blind, placebo-controlled multicentre trial [19], the administration of lornoxicam for four weeks was investigated in patients with osteoarthritis of the hip and the knee.
One hundred and eighty-four patients were randomised; 160 patients were finally included in the intent-to-treat analysis. The dropout rate was quite high – only 117 patients completed the trial. Forty patients under placebo and three groups of 40 subjects each, given lornoxicam in doses of 6mg, 8mg and 12mg per day, were compared.
Outcome: With regard to pain, 8mg and 12mg lornoxicam were significantly better than placebo.
In respect of the Lequesne index which is comparable with the now more commonly used WOMAC score, 6mg and 12mg lornoxicam were significantly better than placebo. In respect of tolerability there was no difference between placebo and lornoxicam administered at a dose of 6mg per day. The groups that were given 8mg and 12mg lornoxicam per day had slightly more side effects compared to placebo, with diarrhoea occurring more frequently under lornoxicam.
In contrast, the frequency of dyspeptic symptoms was approximately the same as that under placebo. The authors of the study conclude that lornoxicam administered in doses of 6mg, 8mg and 12mg per day is effective in patients with osteoarthritis of the hip and the knee. Lornoxicam's tolerability in these doses is better than the estimated tolerability of substances of this category.
In a second randomised multicentre trial [20], lornoxicam administered in doses of 12mg per day (3x4mg) and 16mg per day (2x8mg) was compared with diclofenac 150mg per day (3x50mg) in 135 patients with osteoarthritis of the hip and the knee treated for a period of 12 weeks. Subsequently 85 patients were given lornoxicam for a further 40 weeks in order to document the tolerability and safety of lornoxicam. Outcome: For pain as well as the Lequesne index, no difference was observed between lornoxicam and diclofenac.
In respect of adverse effects there was no major difference between the two substances. Abdominal pain and headaches were slightly more frequent under diclofenac while dyspepsia and diarrhoea occurred more frequently with lornoxicam.

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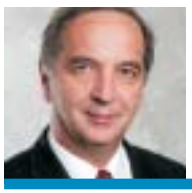

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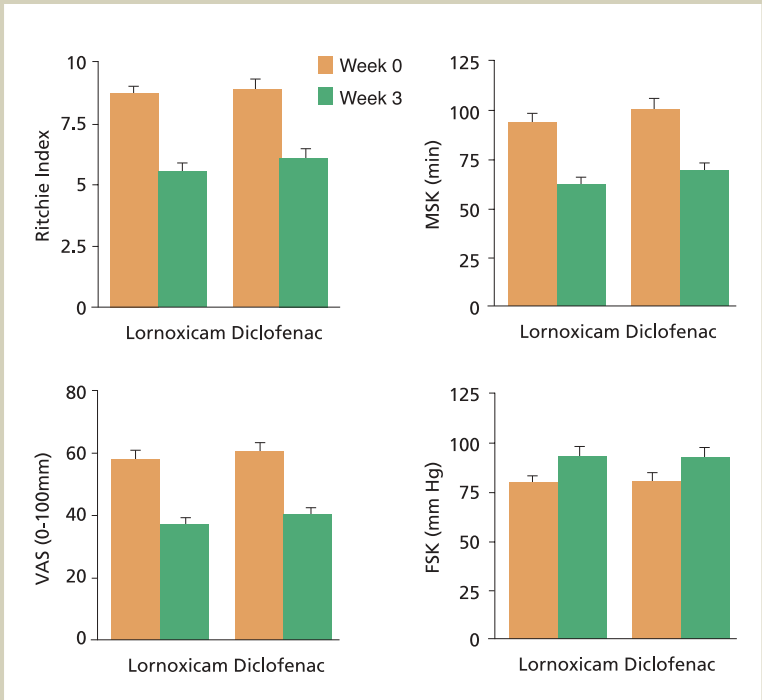
3.2.3 Extraarticular rheumatism

The application of NSAID for this indication is a complex subject. Particularly symptoms like chronic back pain are liable to become a crux as far as treatment is concerned. In 1997 a randomised double-blind trial was performed in six centres in Austria. The patients (n=201) were between 18 and 65 years of age and had low back pain (LBP) for longer than three months. Lornoxicam administered at a dose of 2x4mg per day was compared with diclofenac (2x50mg per day). The primary endpoint of the trial was the response of LBP to the medication. One hundred and ninety patients completed the trial. Outcome: No difference between lornoxicam and diclofenac with regard to efficacy or side effects. For low back pain, lornoxicam administered at a dose of 2x4mg per day is as effective as diclofenac administered 2x50mg per day.

Further possible indications are periarthritis, diseases of tendons, tendon sheaths and the bursa. Lornoxicam may also be used for a wide range of postural disorders and symptoms in the vertebral column secondary to functional disorders, spondylarthritis, and discopathy with and without prolapse.

Figure 6:
Lornoxicam and diclofenac show equal efficacy in rheumatoid arthritis [17]



In a study comprising 96 patients with disk prolapse [22], lornoxicam was compared with morphine administered by a patient-controlled intravenous analgesia (PCA) device after surgery for disk prolapse. PCA had a maximum duration of 24 hours. Outcome parameters were general pain relief, pain relief per hour and hourly differences in the intensity of pain. Both medications proved to be equally effective. Fewer side effects occurred with lornoxicam than with morphine (21.7% under lornoxicam versus 38% under morphine).

3.2.5 General pain management

Although the WHO analgesic ladder for pain management (see Figure 7) is only valid for the treatment of cancer pain, it is significant for all other types of pain therapy as well. NSAID play an important role in all steps of the ladder.
Lornoxicam is advantageous in perioperative pain management because of its short half-life and its short-term effect on platelet aggregation Lornoxicam can be administered without difficulty up to a few hours before the scheduled operation. Manuals for the preparation of surgery mention that any NSAID should be discontinued one week before the operation; this does not apply to lornoxicam.
Lornoxicam is well established in postoperative pain management as well. One of the many reasons is that the substance can be administered by the intravenous route. The fact that lornoxicam can be mixed with certain opioids – specifically tramadol, buprenorphine, and morphine – is an advantage in the management of pain. Lornoxicam should not be mixed with nalbuphine, piritramide, and nicomorphine. ■

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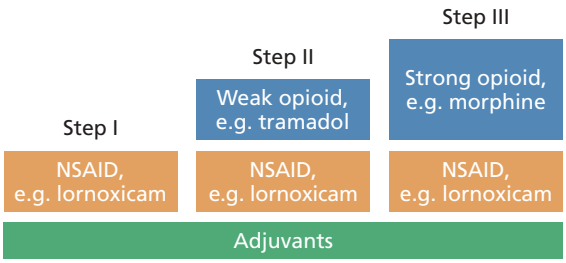
Table 3:
Necessity of renal function controls

Control of renal function under lornoxicam is required
- before major surgical interventions,
- in cases of a pre-existing load on renal function, e.g. due to excessive blood loss or marked dehydration,
- in cases of heart failure,
- during simultaneous treatment with diuretics,
- during simultaneous treatment with drugs with a potential or known nephrotoxic effect.

Figure 7:
WHO analgesic ladder for pain management



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